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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,063	MCHALE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) *22 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary amendments were received and entered as Paper Nos. 13 and 15, respectively, on 12/2/02 and 7/3/03.

An information disclosure statement was received and entered as Paper No. 7 on 8/6/01.

Claims 1-23 are pending in the Application.

Drawings

Applicant has submitted informal drawings which are not be acceptable for publication, should allowable subject matter become apparent. Applicant is encouraged to submit formal drawings for review. In particular, Figures 2A and 3 are of insufficient quality to determine which curve is assigned to which data set. Fig. 13 panels A-D are of insufficient quality to interpret. In Figure 15, it is unclear where the data concerning % of cells remaining ends and the prediction begins, i.e. it is unclear how many data points were actually taken, and which ones were just predicted.

Claim Objections

Claim 2 is objected to because the phrase "[t]he a method" is ungrammatical.

Claim 19 is objected to because it is ungrammatical. Deletion of the word "of" is suggested.

Claims 22 and 23 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple

dependent claim. See MPEP § 608.01(n). Claims 22 and 23 depend from any of claims 1-21, of which claims 12-14, and 18-21 are multiply dependent. Accordingly, the claims 22 and 23 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6, 7, and 9-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 6, and 12 are indefinite because it is unclear what is the distinction between a "method" and a "use". Claims 3 and 6 are also indefinite because they recite "[the] use" without antecedent basis. Because methods and uses are recited as alternatives, they are considered to be non-identical. However, none of the claims from which claims 3 and 6 depend provides an antecedent for a "use". Deletion of "or use" is suggested.

Claims 6, 7, 9-12, and 19 are indefinite because they recite "the sensitisation of the red blood cell" without proper antecedent basis. While the specification teaches at page 9, lines 9-15 that "electrosensitization" and "sensitization" can have the same meaning, it is not clear that they must have the same scope, so it is not clear that "the sensitisation" of claims 6 and 7 is equivalent to the electrosensitization recited in the claims from which they depend.

Claims 8, 13, 14, and 18-21 are indefinite because they recite "the sensitised red blood cell" without proper antecedent basis. While the specification teaches at page 9, lines 9-15 that "electrosensitization" and "sensitization" can have the same meaning, it is not clear that they must have the same scope, so it is not clear that the electrosensitized cell and the sensitized cell of claim 8 are the same cell.

Claim 11 is indefinite because it recites "the electric pulse" without antecedent basis.

Claims 15-21 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims recite no step in which delivery to a target site is achieved.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively disrupting with ultrasound an electrosensitized red blood cell containing an agent loaded in vitro by methods selected from the group consisting of electroporation, sonoporation, microinjection, membrane intercalation, microparticle bombardment, lipid-mediated transfection, osmosis, osmotic pulsing, diffusion, endocytosis, and cross linking to a red blood cell surface component, does not reasonably provide enablement for methods of selectively disrupting with ultrasound an electrosensitized red blood cell which have not been

loaded with an agent, or for methods requiring loading of agents into red blood cells in vivo, or for methods requiring loading of agents into red blood cells by viral infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3 and 12 are drawn to methods of selectively disrupting by ultrasonic treatment red blood cells that have been electrosensitized. The scope of these claims embraces both red blood cells that have been loaded with an agent, and red blood cells that have not been so loaded. However, the specification discloses no use for selectively lysing red blood cells unless these cells have first been loaded with an agent for delivery. See for example the Summary of the Invention at pages 2-4 of the specification. There is no immediately apparent reason that one would wish to selectively lyse electrosensitized red blood cells that do not contain any agent for delivery, and the specification teaches none. Thus one of skill in the art would have to discover some useful reason to selectively lyse unloaded electrosensitized red blood cells, and the experimentation required to do this is considered to be undue. This portion of the rejection can be overcome by incorporating into claim 1 the limitations of claim 4.

The remainder of the rejection pertains to the enabled scope of red blood cell loading techniques.

The claimed invention embraces a variety of methods of loading an agent into red blood cells. The specification teaches at page 12, lines 17-24 that iontophoresis

may be used to load agents into red blood cells, and points out that iontophoresis may be used to deliver an agent across the skin. So, it is reasonable to interpret the claims as embracing a process of loading red blood cells in vivo, unless otherwise limited. Only claim 9 excludes the scope of loading in vivo by limiting the loading process to in vitro or ex vivo embodiments.

While the specification teaches that iontophoresis may be used to deliver charged molecules across a biological membrane such as the skin, it provides no guidance as to how to use iontophoresis, or any other delivery technique, to load an agent into a red blood cell in vivo. Various claim embodiments also require that the cells into which the agent are loaded must be sensitized before, during, or after loading. Guidance in the specification regarding in vivo loading of agents is limited to reference to WO 97/49450. See page 12, lines 23 and 24. However, Applicant is reminded that in any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See MPEP608.01(p), and In re Fouche, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). In any case, while WO 97/49450 is concerned with delivery of agents to intravascular tissues, it provides no guidance as to how to deliver agents to red blood cells, focusing instead on delivery into blood vessels. The instant specification offers no guidance as to how to identify in vivo in the circulation sensitized blood cells, and subsequently load agents into these cells in vivo. Similarly, it fails to teach how to identify in vivo in the

circulation blood cells into which agents have been loaded and how to subsequently sensitize them in vivo. Finally, the specification provides no guidance as to how to perform sensitization and loading simultaneously in vivo.

Claim 21 explicitly recites cell loading procedures including "viral infection". This claim is multiply dependent on each independent claim, so all claims are considered to embrace this embodiment. The specification does not define "viral infection", however Fields et al (In Fundamental Virology, Second Edition, Raven Press, New York, 1991) define this term as "viral multiplication in an infected host". See page 3, line 5 of paragraph bridging columns 1 and 2. It is well known in the art that mammalian red blood cells lack a nucleus, and therefore lack the ability to carry out processes necessary for viral multiplication, e.g. replication of the viral genome, expression of viral genes, and assembly of viral capsids. Further, while it is known that some organisms, such as birds, have nucleated red blood cells, the Examiner is unaware of any virus that infects red blood cells, and a search of the prior art failed to reveal any such virus. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the

> enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the specification fails to disclose the conditions under which agents can be loaded into cells in vivo, and fails to disclose any specific virus that can be used to deliver any agent to a red blood cell by infection. These conditions and materials cannot be considered minor details that can be omitted in the process of providing an enabling disclosure, and a search of the prior art indicates that these conditions and materials are not well known and routinely used in the art. For these reasons, one of skill in the art would have to perform undue experimentation in order to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4, 14-19, 36-40, 43, and 45-47 of copending Application No. 09/748,789. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Both the instant application and 9/748,789 are assigned to Gendel Limited, but these applications have different inventive entities.

'789 teaches a method for selectively releasing an agent from a red blood cell comprising the steps of: (a) pre-sensitising a red blood cell in vitro or ex vivo; (b) loading said red blood cell with an agent; (c) electrosensitising said red blood cell in vitro or ex vivo; and (d) effectuating substantial release of said agent from said sensitised red blood cell by applying ultrasound at a frequency and energy sufficient to cause disruption of sensitised red blood cells. See claim 4 as amended on 3/17/03.

The scope of this method is not exactly identical to that of the instant claims because the instant claims require no pre-sensitising step, and it is unclear if the scope of "substantial release" is equivalent to that of releasing. Because the scopes are not identical, an obviousness type double patenting rejection, rather than a statutory double patenting rejection, is proper.

The method of claim 4 of '789 renders obvious the methods of instant claims 1, 4, and 8 because each of the steps of instant claims 1, 4, and 8 is recited in claim 4 of '789, with "effectuating substantial release of said agent" considered to render obvious the instantly claimed step of "causing the agent to be released".

It would have been obvious to deliver electrosensitize cells by delivery of electric pulses, as required by instant claim 2, because claim 38 of '789 suggests that this should be done.

It would have been obvious to use pulses in the range of 0.1kV/cm to 10kV/cm as required by instant claims 3, 11, and to use pulse lengths between 1 microsecond and 100 milliseconds as required by instant claim 12, because claims 14, and 15 of '789 suggest that this should be done.

It would have been obvious to load the cells either before or after sensitizing, as required by instant claims 5, 6, 19, and 20, because claims 16, 17, 36, and 37 of '789 suggest that this should be done.

Although claims 14-17, 36 and 37 of '789 do not explicitly recite methods of releasing an agent, these claims are drawn to methods of preparing a cell containing an agent, and it would have been obvious to perform these steps in the method of claim 4 of '789 which requires preparing a cell containing an agent.

Instant claims 7 and 10, drawn to methods requiring simultaneous loading and senstization of cells, are considered to be obvious because claim 4 of '789 sets no limitations on the order of loading and sensitisation steps, and the specification of '789 at paragraph 95 teaches that these steps may be carried out simultaneously.

It would have been obvious to perform the loading step of '789 claim 4 in vitro or ex vivo, as required by instant claim 9, because the specification of '789 teaches that this is the preferred method of loading. See paragraph 86. The limitations of instant

claim 13 and 14, regarding the use of diagnostic and therapeutic ultrasound, and the power density of the ultrasound, are taught by claims 18 and 43-47 of '789.

It would have been obvious to modify the method of claim 4 of '789 to deliver an agent to a particular target site in a vertebrate because the specification teaches at paragraph 103 that the ultrasound is preferably applied to a target site. This would necessarily result in delivery of at least some of the agent to the target tissue.

It would have been obvious to modify the methods of claims 4 and 15 of '789 to include PEG on the surface of the red blood cells, as required by instant claim 16, and to introduce the red blood cell into a mammal as required by instant claim 17, because the specification of '789 at paragraph 72 teaches that this may be done.

It would have been obvious to modify the methods of claims 4 and 15 of '789 to allow loading of the agent during, after, or before electrosensitization, as required by instant claims 18-20 respectively, because claims 16 and 17 of '789 teach that loaded, sensitized cells may be prepared by loading before or after sensitization, and because the specification at paragraph 95 teaches that any of these loading and sensitisation sequences may be used.

It would have been obvious to modify the method of claim 4 of '789 by using any one of the loading procedures recited in instant claim 21 because claim 4 of '789 places no limitation on the type of loading procedure employed, and the specification teaches at paragraph 82 that any of the loading procedures recited in instant claim 21 may be used.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

All claims are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER